DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
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STATEMENT OF

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U.S. FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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COMMITTEE ON
GOVERNMENT REFORM

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INTRODUCTION

Mr. Chairman and members of the Committee, I am Dr. Steven Galson, Acting Director of the Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the relationship between CDER's Office of New Drugs (OND) and Office of Drug Safety (ODS) within the context of FDA's pre-market and post-market drug approval process, as well as recent Agency initiatives regarding drug safety.

SAFETY IS A HIGH PRIORITY

Modern drugs provide unmistakable and significant health benefits. FDA's drug review process is recognized worldwide as a gold standard. Indeed, we believe that FDA maintains the highest standards for drug approval. There have been significant additions to those standards during the last several decades, in response to advances in medical science. Currently, FDA approves drugs after they are studied in many more patients and undergo more detailed safety evaluations than ever before. It is not always recognized, but at least half of the effort of FDA's pre-market reviewers is dedicated to the assessment of safety. Major changes have taken place in how drugs are evaluated, including a complete evaluation of their metabolism, their interactions with other drugs, and potential differences of effectiveness or safety in people of different genders, ages, and races. In addition, internal guidance now describes an approach to the systematic assessment of safety that yields a comprehensive review, focusing on the potential problems with the greatest clinical importance.

FDA grants approval to drugs after a sponsor demonstrates that their benefits outweigh their risks for a specific population and a specific use, and that the drug meets the statutory standard for safety and efficacy. However, no amount of study before marketing will ever elucidate all the information about effectiveness or all the risks of a new drug. FDA recognizes that there is no way we can anticipate all possible effects of a drug from the clinical trials that precede approval. That is why Congress has supported and FDA has created a post-market drug safety program designed to collect and assess adverse events identified after approval. The role of our post-marketing safety system is to detect serious unexpected adverse events and take definitive action when needed.

FDA uses information from post-marketing clinical trials, adverse event reports filed by drug manufacturers, spontaneous reporting of adverse events by physicians, pharmacists, and consumers, and observational studies to identify problems in marketed products. FDA staff monitors this information and looks for emerging patterns. The Agency initiates action as needed.

THE DRUG APPROVAL PROCESS

Pre-Approval Focus on Safety

FDA's focus on safety begins at the earliest stages of drug development. Before beginning any human trials, the sponsor must perform extensive animal toxicity studies. Animal studies provide guidance on initial dosing and point to areas of safety needing special attention during human studies. Researchers closely monitor these studies and FDA reviews results in detail to be sure that giving the drug to humans is safe. FDA's oversight becomes more robust when human testing begins and we review a product under an investigational new drug application (IND). During the IND period, products usually undergo three phases of clinical (human) trials. Phase I studies involve the initial introduction of a drug into humans to assess the most common side effects and examine the range of doses that patients can take safely without a high rate of side effects.

Phase I studies also gain information on drug kinetics and metabolism, drug-drug interactions, and, often, on the effects of the drug on the electrocardiogram. Phase I trials may be in patients with the disease the experimental drug is being developed to treat, but also may be in healthy volunteer subjects. In general, these studies yield initial safety data and useful information to establish the appropriate dose of the drug.

Phase II of drug development includes the earliest controlled clinical studies of the effectiveness of the drug for a specific indication in patients with the disease or condition. This phase of testing also identifies short-term, relatively common side effects of the drug. Phase II studies are typically well controlled and closely monitored and may involve up to several hundred patients. In these studies, researchers compare results of patients receiving the drug with those who receive a placebo, a different dose of the test drug, and/or another active drug. At the conclusion of these studies, FDA and the sponsor usually meet to determine how the drug's development should be studied in Phase III and how to design and conduct further trials.

Researchers design Phase III trials for a larger number of patients and build on the data gained from the first two phases of trials. These studies provide the additional information about safety and effectiveness needed to evaluate the overall benefit-risk relationship of the drug. The larger number of patients (typically several thousand) allows detection of less frequent adverse events. The larger number of patients (typically 300-600) exposed for more than 6 months allows detection of adverse events that develop only after longer exposure. Phase III study designs establish the basis for extrapolating the results to the general population. It is results of these studies that usually provide essential information for the package labeling. Once the results of all the clinical trials are available, the sponsor of the application (usually the manufacturer of the product) analyzes all the data and submits a new drug application (NDA) or biologics license application (BLA) to FDA for review and approval to market the product in the U.S.

Pre-marketing assessment of the safety aspects of an application is critical to the determination of whether a drug can be approved and this assessment represents about half of the effort involved in a review, both in time spent and in documentation. To assure a complete and consistent review of safety of an NDA or BLA, in February 2005, FDA issued a guidance to reviewers for conducting and preparing reports of clinical safety reviews. See *http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4143B1_06_Tab-13.pdf*. This document is a collaborative effort across various offices in CDER, including OND and ODS. The guidance assists reviewers conducting the clinical NDA/BLA safety reviews, describes good review practices for pre-marketing safety reviews, provides standardization and consistency of format and content of safety reviews, and ensures that critical presentations and analyses of safety data are not omitted.

Post-Approval Risk Assessment

Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit safety updates to FDA on their drug. These updates are submitted in an expedited fashion for serious and previously unidentified risks, and periodically for less urgent safety issues. These reports include reports of adverse events of which the company has been informed, as well as new study results that are available whether published or not (including those published in other countries). Also during this period, we continuously receive adverse event reports directly from sources such as health care providers and patients through our own MedWatch program. Expedited adverse event reports from sponsors or MedWatch are stored in a common computerized database along with components of the periodic reports for selected drugs. FDA epidemiologists and safety evaluators review and analyze the reports to assess the frequency and seriousness of the adverse events. Our response to information from this ongoing surveillance depends on an evaluation of the aggregate public health benefit of the product compared to its evolving risk profile.

Decisions about regulatory action in response to evidence of a drug safety risk are complex, taking into account many factors. The occurrence of a rare event, even a serious event, may or may not, by itself, be sufficient to take a drug product off the market. If the public health benefit of the product outweighs its known risks, FDA generally allows the continued marketing of the drug. Often, as more becomes known about the potential risks or benefits of a product, its label will be revised so that it better reflects information on appropriate use. For example, FDA may ask the manufacturer to revise the labeling to add information on adverse reactions not previously listed, to add new warnings describing conditions under which the drug should not be used, or to add new precautions advising doctors of measures to minimize risk. FDA often issues Public Health Advisories and information sheets for health care providers and patients that discuss the new safety information. In the event of reports of death or life-threatening injury, FDA and the sponsor may consider restricting the distribution of the product or removing it from the market.

Our action will depend on the characteristics of the adverse events, the frequency of the reports, the seriousness of the diseases or conditions for which the drug provides a

benefit, the availability of alternative therapy, and the consequences of not treating the disease. Detection and limiting adverse reactions can be challenging. Weighing the impact of adverse drug reactions against the benefits of a particular product is multifaceted and complex, and involves scientific as well as public health issues.

Attachment A contains the sequence of events with Vioxx from the opening of the IND on December 20, 1994, until the public announcement of worldwide withdrawal on September 30, 2004, and also may be found on FDA's website at *http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_04_E-FDA-TAB-C.htm*. This document demonstrates the give and take between the Agency and sponsors in negotiating labeling changes when adverse events occur that warrant Agency action.

Independent Offices in CDER Foster Critical Communication and Cooperation

A sound program for assessing the safety of drugs, particularly weighing risks against benefits, demands integrated expertise from a variety of disciplines and perspectives. In CDER, physicians, pharmacists, toxicologists, chemists, epidemiologists, statisticians, bio-pharmaceutics experts, and clinical pharmacologists share drug safety assessments. These experts work in many organizational components of the Center, but predominantly in OND and ODS. These offices work closely together, but are in different organizational components of the Center, thereby ensuring their reporting and operating independence. As in any scientific organization, the ability for scientists to develop independent perspectives on a given issue and bring consensus to decisions depends on strong communication at all working levels, leadership and a sense of shared responsibility.

Safety assessments in any given drug's life cycle begin in OND, where toxicologists and physicians review the animal data in support of Phase I studies, as well as each clinical study protocol and results of the studies in Phases I, II and III before a drug is marketed. Such assessments consider results of new animal studies beyond those that were used to justify initial clinical trials; reports of serious adverse events occurring in clinical studies that are submitted to FDA within days of their occurrence; results of studies of how a drug is metabolized once in the body; monitoring of the medical literature for current thinking about the drug as it may have been used in other countries, and many other sources of information. FDA staff conducts detailed reviews of all these sources and more before FDA approves a product for marketing. FDA will not approve a drug if its benefits in clinical trials are not thought to outweigh its risks as seen in the trial or if the clinical trials did not adequately assess safety.

There are times when a drug is approved, but CDER remains concerned that a particular aspect of its safety profile needs to be explored in more depth. These concerns might include, for example, a sub-population of patients who were not well represented in the pre-market studies, a question about how well the drug is tolerated in combination with other commonly prescribed drugs, or how the safety of the drug compares to a different drug to treat the same condition. In such cases, when we grant approval for marketing,

we request a formal commitment from the sponsor to conduct such a study within a specified timeframe after approval.

CDER's OND has authority for making decisions about whether a product will be approved for marketing. OND is organized into 17 divisions that represent clinical areas of expertise, such as oncology, endocrinology, psychiatry and pulmonary medicine. Products are reviewed by the division that contains experts in the field of medicine that will primarily be the users of the product (e.g., asthma drugs would be reviewed by the division with pulmonary expertise). Pre-market safety assessments are often shared across divisions. When a drug being assessed in one division appears to have a side effect that might be better evaluated by a different type of clinical expert, an expert in another division will be consulted (e.g., an antibiotic might cause lung toxicity, so the pulmonary division would be consulted).

Also, at the time of reviewing an NDA for marketing approval, the OND review team routinely engages ODS in discussing the overall safety profile of the drug, and often requests their assistance in deciding what types of post-marketing studies should be requested of the company to address residual concerns. ODS' involvement in the review of a drug before marketing is particularly critical when the drug has a risk profile that warrants a complex risk management plan, such as a restricted distribution program or specialized educational tools for patients or health care providers about how best to use the drug.

Once a product is on the market, a sponsor may decide to study the drug for additional indications. In such a case, the application is in "pre-market" status regarding the new indication at the same time we are conducting post-market surveillance of the marketed product. This means that clinical study data, including adverse event reports from trials, will be submitted on a continuous basis and new studies for even more new indications or in new populations for the original indication may be started. All of these studies require review and monitoring by OND. At the same time, ODS continues to monitor the safety of the drug based on post-marketing adverse event reports that are submitted by companies or directly to FDA through the MedWatch program, all of which must be factored into decisions about design of the new studies and whether to approve new uses for the drug. ODS completes about 1300 safety reviews a year as well as participates in the development and review of over 40 risk management plans in close collaboration with OND.

When post-market surveillance data cannot answer an important safety question about a drug or group of drugs, ODS has independent authority to pursue its own epidemiology research. This independent research is highly valued in the scientific community when it conforms to accepted scientific standards and procedures such as sound scientific oversight and peer review. Research conducted by ODS epidemiologists employs a program of cooperative agreement mechanisms and contracts that allow FDA to have access to databases about drug usage and effects and to partner with non-government researchers to do the studies.

Factoring identified risks, whether from clinical trials, adverse event reports or epidemiology studies into the risk-benefit equation for a drug requires cooperation

between OND and ODS. Each office offers expertise in evaluating the risk-benefit profiles of marketed drugs. OND is equipped to evaluate the NDA, including the clinical trial data, labeling information, and post-marketing studies. ODS brings unparalleled ability to identify emerging risks in new patient populations that may not have been seen during pre-market clinical trials. It is only through the contributions of these two offices that the most accurate assessment of a drug's risk-benefit profile can be made.

The Agency believes CDER's current organizational structure has significant benefits. Having both independent offices in FDA's CDER ensures efficient decision-making, expeditious resolution of disputes and the rapid dissemination of critical drug safety information to the public and health care providers.

Turning Risk-Assessment into Action—Joint Efforts of OND and ODS

Recent events related to the safety profile of non-steroidal anti-inflammatory drugs are illustrative of the critical roles of both OND and ODS in arriving at sound scientific decisions and public health policy on regulatory actions for drugs.

On April 7, 2005, FDA issued a Public Health Advisory to inform the public and health care community of a series of important changes pertaining to the marketing of the non-steroidal anti-inflammatory class of drugs (NSAIDs), including COX-2 selective and prescription and non-prescription (over-the-counter (OTC)) non-selective NSAID medications. After carefully considering the available data on all of the NSAIDs, including the presentations, discussions, and votes from the joint public meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on February 16, 17, and 18, 2005, FDA took action to immediately address the cardiovascular (CV) safety concerns for these drugs along with their overall risk-benefit profile. FDA's actions are summarized, as follows:

1. FDA asked Pfizer, Inc. to voluntarily withdraw Bextra (valdecoxib) from the market. Pfizer has agreed to suspend sales and marketing of Bextra in the U.S., pending further discussions with the Agency.

2. FDA asked manufacturers of all marketed prescription NSAIDs, including Celebrex, (celecoxib), a COX-2 selective NSAID, to revise the labeling (package insert) for their products to include a boxed warning and a Medication Guide. The boxed warning will highlight the potential for increased risk of CV events with these drugs and the well described, serious, and potentially life-threatening gastrointestinal (GI) bleeding associated with their use. The Medication Guide will accompany every prescription NSAID at the time it is dispensed to better inform patients about the CV and GI risks.

3. FDA asked manufacturers of non-prescription NSAIDs to revise their labeling to include more specific information about the potential GI and CV risks, and information to assist consumers in the safe use of the drug. This announcement

does not apply to aspirin as it has clearly been shown to reduce the risk of serious adverse CV events in certain patient populations.

It was only through shared information and consensus across OND and ODS that these actions were decided. Several examples of this are as follows:

- OND and ODS jointly made the determination that the lack of adequate data on the CV safety of long-term use of Bextra, along with the increased risk of adverse CV events in clinical studies of short-term coronary artery bypass surgery (CABG) suggested that the risk of Bextra was probably relevant to chronic use.

- ODS analyzed post-marketing reports of serious and potentially life-threatening skin reactions, including deaths, in patients using Bextra. The ODS and OND reviews of the reports of these reactions in individual patients led to the consensus that the reaction is unpredictable, occurring in patients with and without a prior history of sulfa allergy, and after both short- and long-term use.

- OND's reconsideration of the original NDA data for Bextra confirmed the lack of any demonstrated advantages for Bextra compared with other NSAIDs.

- It was through much discussion across OND and ODS, including consideration of the advice from two Advisory Committees, that led CDER to conclude that the benefits of Celebrex outweigh the potential risks in properly selected and informed patients. Accordingly, FDA will allow Celebrex to remain on the market as long as a box warning about the GI and CV risks of the drug are implemented.

- It required the different perspectives from OND and ODS, evaluating multiple sources of data, for CDER to conclude that both CV and GI adverse events are likely to be common to the entire class of NSAIDS, new and old (with the exception of CV risk for low-dose aspirin). The importance of the different types of expertise that facilitated that decision-making (clinical trial design and analysis, statistics, clinical pharmacology, pharmacovigilance, epidemiology and clinical medicine) cannot be overemphasized.

The April 6, 2005, summary memorandum, "Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risks," co-signed by John Jenkins, M.D., Director, OND, and Paul Seligman, M.D., Director, Office of Pharmacoepidemiology and Statistical Science (the organizational through which ODS reports) illustrates the close cooperation between the two offices. See Attachment B. This memo also may be found on FDA's website at: *www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf.*

STATUTORY CHANGES ENHANCE DRUG APPROVAL AT FDA

FDA was founded in response to concerns about safety. Attention to safety pervades everything that we do. In the Federal Food, Drug and Cosmetic (FD&C) Act of 1938, Congress gave FDA the authority to review the evidence that a drug was safe for its intended use. In 1962, Congress added a requirement that drug sponsors also demonstrate that a drug is effective, using adequate and well-controlled studies. Thus, drug safety means that the demonstrated benefits of a drug outweigh its known and potential risks for the intended population and use. In recent years, Congress has enacted legislation that provides significant additional tools to improve our focus on safety: the Prescription Drug User Fee Act (PDUFA) and the Food and Drug Administration Modernization Act (FDAMA).

In 1992, Congress enacted PDUFA. This landmark legislation provided significant resources for FDA to hire more medical and scientific reviewers to conduct pre-market reviews, to hire support personnel and field investigators to speed the application review process for human drug and biological products, and to acquire critical information technology infrastructure to support our review process.

In 1997, following the success of PDUFA I, Congress reauthorized the program for an additional five years when it enacted FDAMA. With PDUFA II came additional goals designed to reduce drug development times. In 2002, Congress reauthorized PDUFA for a third time. PDUFA III places great emphasis on ensuring that user fees provide a sound financial footing for FDA's new drug and biologic review process and, for the first time, gives FDA authority to expend PDUFA resources on risk management and drug safety activities during the approval process and during the first two to three years following drug approval.

One of the primary goals of PDUFA was to address the significant delay in U.S. patients' access to new medicines. The objective was to increase patient access to new drugs, without increasing risks. Before PDUFA, the delay in approving drugs in the U.S. was a serious concern for U.S. patients and practitioners. Life-saving drugs were available to patients in other countries months and sometimes years before they were available in the U.S. Because of the additional resources and process improvements implemented since PDUFA I became law, the average FDA drug review time has declined by more than 12 months. While PDUFA gave FDA the resources needed to bring safe and effective drugs to the market faster, it did not change the high standards FDA employs in the review of NDAs. In fact, FDA's review standards remain the gold standard in the world.

A recent study by Berndt, et al. of the National Bureau of Economic Research, found no significant differences in the rates of safety withdrawals for drugs approved before PDUFA compared to drugs approved during the PDUFA era. This research confirms FDA's analysis on the same subject. In addition, as the public has become more aware of drug safety issues, we are now adding box warnings sooner than we did before PDUFA. This indicates that PDUFA has been successful in both speeding access and preserving safety.

In general, PDUFA authorizes FDA to collect fees from companies that produce certain human drug and biological products. When a sponsor seeks FDA approval for a new drug or biologic product, it must submit an application accompanied by a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed. Before PDUFA, taxpayers alone paid for product reviews through budgets provided by Congress. Under the PDUFA approach, industry provides

additional funding in return for FDA's efforts to meet drug-review performance goals that emphasize timeliness but do not alter or compromise our commitment to ensuring that drugs are safe and effective before they are approved for marketing.

PDUFA III – GREATER EMPHASIS ON DRUG SAFETY

As noted above, thanks to PDUFA, we are able to commit far greater resources to our important safety responsibilities. Under PDUFA III, Congress granted authority for FDA to expend user fees for post-market safety review. FDA made this a top priority during our PDUFA negotiations. Beginning with PDUFA III, for drugs approved after October 1, 2002, we can spend PDUFA resources on "collecting, developing, and reviewing safety information on drugs, including adverse event reports" for up to three years after the date of approval. The initiative to address drug safety for PDUFA III products helps FDA better understand a drug's risk profile, provide risk feedback to the sponsors and provide essential safety information to patients and health practitioners.

From October 1, 2002, through December 31, 2004, FDA reviewed 63 risk management plans for drug and biologic products. Twenty-eight of these related to applications submitted after PDUFA III took effect. We also conducted pre-approval safety conferences, risk management plan reviews, drug safety meetings, and meetings with sponsors to discuss proposed drug supplements.

In response to PDUFA III, FDA held a public meeting in April 2003 to discuss risk assessment, risk management, and pharmacovigilance practices. On May 5, 2004, based on the valuable information generated through the meeting process, we published three draft guidances on these important drug safety topics. Following our review of the extensive comments we received about these documents, all three final guidances were published in April 2005.

SAFETY ADVANCES IN FDAMA

Enacted in 1997, FDAMA has been an important addition to FDA's legal framework. FDAMA passed following a thorough Congressional examination of the Agency's policies and programs. It instituted a number of comprehensive changes, reaffirmed the Agency's vital role in protecting the public health and served as the vehicle for enacting PDUFA II.

Pediatric Exclusivity and Safer Use of Drugs in Children

For decades, children were prescribed medications that had not been studied for safety and efficacy in pediatric populations. As a component of FDAMA, Congress provided incentives to sponsors to conduct pediatric clinical trials. Section 111 of FDAMA authorized FDA to grant an additional six months of marketing exclusivity (known as pediatric exclusivity) to pharmaceutical manufacturers that conduct studies of certain drugs in pediatric populations. The objective of section 111 was to promote pediatric safety and efficacy studies of drugs. With the valuable information generated by these studies, the product labeling can then be updated to include appropriate information on use of the drug in the pediatric population. To qualify for pediatric exclusivity, sponsors must conduct pediatric studies according to the terms of a Written Request issued by FDA and submit the results of those studies in an NDA or supplement.

In 2002, Congress renewed this authority when it enacted the Best Pharmaceuticals for Children Act (BPCA). BPCA also mandates that during the one-year period beginning on the date a drug receives exclusivity, FDA review and refer to the Pediatric Advisory Committee, in a public forum, any adverse event reports associated with the use of the drug. To date, we have referred to the Pediatric Advisory Committee at six separate meetings adverse event reports on 34 drugs.

Finally, BPCA contains important, new disclosure requirements. Outside of BPCA, the Agency generally may not publicly disclose information contained in an IND, unapproved NDA, or unapproved supplemental NDA. Once FDA approves an NDA or supplemental NDA, the Agency can make public certain summary information regarding the safety and effectiveness of the product for the approved indication.

However, section 9 of BPCA gives FDA important new disclosure authority. BPCA requires that, no later than 180 days after the submission of a supplement containing studies conducted in response to a Written Request, the Agency must publish a summary of FDA's medical and clinical pharmacology reviews of those studies. Moreover, we must publish this information regardless of whether our action on the pediatric supplement is an approval, approvable, or not-approvable action. Thus under FDAMA, information on pediatric studies conducted in response to Written Requests was not available until after the supplemental application was approved. In contrast, under BPCA, a summary of FDA's medical and clinical pharmacology reviews of pediatric studies is publicly available regardless of the action taken on the supplemental application. Since 2002, FDA has posted the summaries of these reviews for 41 products submitted in response to a Written Request on FDA's website at: *http://www.fda.gov/cder/pediatric/Summaryreview.htm*. This information provides a rich source of valuable safety information to allow pediatricians to make more informed decisions about whether and how to use these drugs in their patients.

Post-Marketing Safety Studies

On April 30, 2001, FDA's regulations implementing section 130 of FDAMA, which requires sponsors of approved drugs and biologics to report annually on the status of post-marketing commitments, became effective. These regulations modified existing

reporting requirements for NDA drug studies and created a new reporting requirement for biologic products.

FDA may request that a sponsor conduct post-marketing studies to provide additional important information on how a drug works in expanded patient populations or to identify safety issues that occur at very low frequency or in special patient populations. Patient and consumer advocates who track the completion of post-marketing commitments and FDA's efforts to review study results and modify drug labeling are keenly interested in the post-marketing safety study reporting obligations in section 130. The regulations implementing section 130 provide FDA with a mechanism to monitor study progress through the annual submission of study status reports. FDA posts the status of post-marketing studies on its public website and publishes an annual summary of industry's progress in fulfilling post-marketing commitments in the *Federal Register*.

CRITICAL PATH

On March 16, 2004, FDA released a report addressing the recent slowdown in innovative medical therapies submitted to FDA for approval: "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." See, *http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html*. The report describes options to modernize the medical product development process to try to make it more predictable and less costly. The report focuses on ways that FDA could collaborate with academic researchers, product developers, patient groups, and other stakeholders to make the critical path much faster, predictable, and less costly. Improved safety tools and tools to help individualize therapy are integral parts of the Critical Path.

Enhancing the Safety of Medical Products

During drug development, safety issues should be detected as early as possible. However, because of limitations of current methods, safety problems are often uncovered only during clinical trials or, occasionally, after marketing. Some tools used for toxicology and human safety testing are outdated despite efforts to develop better methods. Clinical testing, even if extensive, often fails to detect important safety problems, either because they are uncommon or because the tested population was not representative of eventual recipients. Conversely, some models create worrisome signals that may not be predictive of a human safety problem.

There are opportunities for developing tools that can more reliably and efficiently determine the safety of a new medical product. To meet this challenge, FDA has called for a new focus on modernizing the tools that applied biomedical researchers and product developers use to assess the safety and effectiveness of potential new products. Many of these tools—diagnostics such as pharmacogenomic tests and imaging techniques—would also be used after marketing to monitor safety in the real world clinical setting. The Critical Path report describes opportunities for FDA, working with academia, patient groups, industry, and other government agencies, to embark on a collaborative research effort. The goal is to create new performance standards and predictive tools that will

provide better answers about the safety and effectiveness of investigational products, to do this faster and with more certainty, and to enhance the safety of these products in the clinic.

In addition to improved safety tools, Critical Path also focuses on tools that will help individualize therapy. We enhance safety when the target population does not include individuals who cannot benefit from the treatment. For these individuals, drug exposure is all risk. Better tools for individualized therapy will help to identify patients who will respond to therapy and, very importantly, keep those who are at high risk for serious side effects from receiving the therapy. New science has provided the basic knowledge to make these tools a reality.

Critical Path is not a fundamental departure for FDA, but rather builds on the Agency's proven "best practices" for expediting the availability of promising medical technologies. While the report touches on all aspects of medical product development, identifying new tools to address drug safety challenges would represent a giant step down the Critical Path.

NEW FDA INITIATIVES TO STRENGTHEN DRUG SAFETY

November 2004 Five-Step Plan

At FDA, we are constantly striving to improve our processes and methods, and thereby better serve the public health. Recent developments have prompted us to refocus our drug safety efforts and take additional steps to identify drugs that may have unacceptable risk profiles.

On November 5, 2004, Acting FDA Commissioner Lester Crawford announced a five-step plan to strengthen FDA's drug safety program. First, it called for FDA to sponsor an IOM study to evaluate the current drug safety system. An IOM committee will study the effectiveness of the U.S. drug safety system, with an emphasis on the post-marketing phase, and assess what additional steps FDA could take to learn more about the side effects of drugs as they are actually used. We have asked IOM to examine FDA's role within the health care delivery system and recommend measures to enhance the confidence of Americans in the safety and effectiveness of their drugs. In recent weeks, the IOM announced the names of the experts who will conduct the study. We are confident that this distinguished panel will provide a thorough review of the drug safety system in this country and advise FDA on how to help ensure that drug safety assessments keep pace with other aspects of drug development.

Second, Dr. Crawford announced that CDER would implement a program for addressing differences of professional opinion. I am pleased to report that CDER has put this program into effect. In most cases, free and open discussion of scientific issues among review teams and with supervisors, managers and external advisors, leads to an agreed course of action. Sometimes, however, a consensus decision cannot be reached, and an employee may feel that his or her opinion was not adequately considered. In an effort to

improve the current process, CDER has formalized a program to help ensure that the opinions of dissenting scientific reviewers are formally addressed and that FDA's decision-making process is transparent. An ad hoc panel, including FDA staff and outside experts not directly involved in disputed decisions, will have 30 days to review all relevant materials and recommend to the Center Director an appropriate course of action.

Third, CDER is conducting a national search to fill the currently vacant position of Director of the Office of Drug Safety, which is responsible for overseeing the post-marketing safety program for all drugs. CDER is seeking a candidate who is a nationally recognized drug safety expert with knowledge of the basic science of drug development and post-marketing surveillance, and a strong commitment to protecting the public health. CDER is working with the Office of Personnel Management on this search.

Fourth, in the coming year CDER will conduct additional workshops and advisory committee meetings to discuss complex drug safety and risk management issues. Most recently, for example, the Agency conducted a three-day Advisory Committee meeting that examined COX-2 selective NSAID drugs and related medicines. This meeting was held on February 16-18, 2005, and more than twenty-five experts made presentations. At the end of the meeting, the Advisory Committee issued recommendations that the Agency promptly and carefully reviewed before announcing a proposed regulatory action discussed below.

Finally, as promised by Dr. Crawford in his November announcement, FDA has now published final versions of three guidances that the Agency developed to help pharmaceutical firms manage risks involving drugs and biological products. These guidances will assist pharmaceutical firms in identifying and assessing potential safety risks before and after a drug reaches the market.

February 2005 Drug Safety Announcement

On February 15, 2005, Health and Human Services (HHS) Secretary Michael Leavitt and Acting FDA Commissioner Crawford unveiled a new, emboldened vision for FDA that will promote a culture of transparency, openness, and enhanced oversight within the Agency. As part of this vision, FDA plans to create a new Drug Safety Oversight Board (DSB) to provide independent oversight and advice on the management of important drug safety issues and to manage the dissemination of certain safety information through FDA's website to health care professionals and patients.

Under this proposal, FDA plans to enhance the independence of internal deliberations and decisions regarding risk/benefit analyses and consumer safety. The DSB will oversee the management of important drug safety issues within CDER. The DSB will include individuals from FDA, as well as medical experts from other HHS agencies and government departments (e.g., the National Institutes of Health and Department of Veterans Affairs). Individuals on the Board who have conducted the primary review of data or served as deciding officials for any regulatory action under consideration will be recused from voting on issues concerning those particular drugs. CDER's Deputy Director will serve as the Chair of the DSB. The DSB also will consult with other

medical experts and representatives of patient and consumer groups. CDER is updating its Manuel of Policies and Procedures (MAPP) to reflect the organizational structure, roles, and responsibilities of DSB in CDER. Among other responsibilities described in the MAPP, the DSB and its staff will:

- Identify, track, and oversee the management of important drug safety issues;
- Adjudicate organizational disputes concerning the management of drug safety issues;
- Establish policies regarding management of drug safety issues in CDER;
- Select drugs to be placed on Drug Watch (described below) and update their status (including deciding to remove drugs from Drug Watch) as appropriate;
- Oversee the development of patient and professional information sheets in CDER;
- Track important emerging safety issues and ensure that they are resolved in a timely manner; and
- Ensure that CDER decisions about a drug's safety benefit from the input and perspective of experts within and outside FDA who have not conducted the primary review or served as a deciding official in the ongoing pre-market evaluation or post-market surveillance activities with respect to that drug.

FDA also plans to increase the transparency of the Agency's decision-making process by establishing new and expanding existing communication channels to provide drug safety information to the public. These communications will help ensure that established and emerging drug safety data are quickly available in an easily accessible form. The increased openness will enable patients and their health care professionals to make better-informed decisions about individual treatment options.

One communication mechanism the Agency is proposing is a new *Drug Watch* web page that will include emerging information about possible serious side effects or other safety risks for previously and newly approved drugs. This resource will contain valuable information that may affect patient selection or monitoring decisions. The web resource may also contain information about measures that patients and practitioners can take to prevent or mitigate harm. This information resource will significantly enhance public knowledge and understanding of safety issues by discussing emerging or potential safety problems, sometimes even before FDA has reached a conclusion that would prompt a regulatory action.

We are also intensifying our current efforts to provide the public with the most important information for the safe and effective use of drugs in patient-friendly language. We are doing this through the development of two tools: *Patient Information Sheets* and *Healthcare Professional Information Sheets*.

1. *Patient Information Sheets* are intended to convey critical facets of a product's approved labeling in lay terms. These sheets will also include a section for "emerging safety information" in those instances when we determine that there is information on the *Drug Watch* that a patient should consider. This "emerging safety information" will match the information on the *Drug Watch*. Information from the *Drug Watch* that is not in the final labeling of the product will be clearly

identifiable and accompanied by a disclaimer, such as: *"This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available."* Our ultimate objective is to develop Patient Information Sheets for all approved drugs, most of which will not have an emerging safety section.

2. *Healthcare Professional Information Sheets* are intended to highlight the most up-to-date information practitioners may want to consider in prescribing drugs for their patients. We ultimately intend to develop these sheets for all new molecular entities as well as some other drugs. This is not a new approach. When available, the highlights section of a product's approved labeling will be used to develop the *Healthcare Professional Information* sheets.

We have already posted some patient and *Healthcare Professional Information* sheets on our website for drugs with recent emerging safety issues. See for example, Celebrex patient and professional sheets, *http://www.fda.gov/cder/drug/infopage/celebrex/Celebrex-ptsk.pdf* and *http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.pdf*. We intend to link the information that is on *Drug Watch* to patient and *Healthcare Professional Information* sheets when they are available.

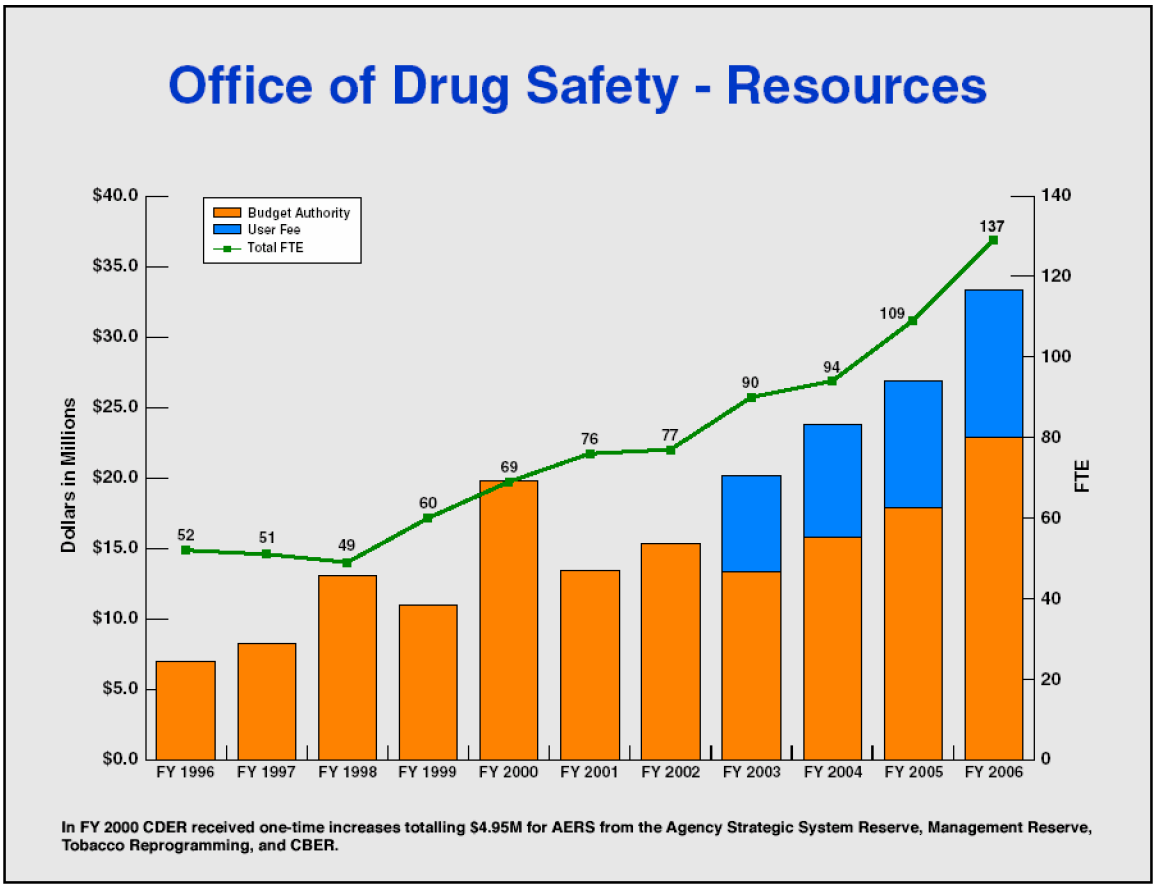
As FDA develops these communication tools, the Agency will solicit public input on how FDA should manage potential concerns associated with disseminating emerging information prior to regulatory action. In addition, FDA will actively seek feedback from health care professionals, patients and consumers on how best to make this information available and useful to them.

Increased Funding for the Office of Drug Safety (ODS)

FDA has a longstanding commitment to drug safety. CDER devotes more than 50 percent of its current resources to critical regulatory activities to ensure drug safety throughout the entire life cycle of U.S. pharmaceuticals. Drug safety analysis is a collaborative effort by various offices across CDER. ODS is one such office involved in the overall drug safety function, with a primary focus on the evaluation of drug safety post-marketing. The graph, set forth below, demonstrates the steady increase in ODS' financial and human resources over the past decade.

The budget for fiscal year 2006 continues this commitment. The President has proposed a 24 percent increase for FDA's post-market safety program to help further ensure that America's pharmaceutical supply is safe and effective, and of the highest quality. Under this proposal, ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such as risk management, risk

communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. The Administration's proposed budget for ODS will increase by $6.5 million, including $1.5 million in user fees, for a total fiscal year 2006 ODS funding level of $33.4 million. PDUFA resources will represent nearly one-third of the ODS budget for the coming year. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.



With the additional funds, FDA expects to be able to hire eight additional Full Time Equivalents (FTEs) in ODS to establish policies and processes regarding safety reviews and risk management, to manage communications with OND and to support patient safety initiatives and external partnerships with CMS, AHRQ, and other HHS Agencies.

We also plan to hire an additional 14 FTEs in the three operating divisions of ODS. These employees will handle the increased workload of monitoring biologic therapeutics; promote increased communication and coordination of safety review activities within the divisions; increase focus on medical error signal detection; increase epidemiological expertise to explore safety risks and signals in various population databases; and manage the increasing workload in ODS for new drug consultations and designing post-approval studies for new drug use in specific populations.

Finally, we plan to hire six FTEs to increase staff dedicated to evaluating and communicating drug safety risks to the health care community and the American public.

CONCLUSION

At FDA, providing the American public with safe and effective medical products is our core mission. We base decisions to approve a drug, or to keep it on the market if new safety findings surface, on a careful balancing of risk and benefit to patients. This is a multifaceted and complex decision process, involving scientific and public health issues. The recent initiatives we have announced will improve our current system to assess drug safety. Moreover, we will continue to evaluate new approaches to advance drug safety. As always, we value input from Congress, patients and the medical community as we develop and refine these drug safety initiatives.

While FDA can do its part by providing accurate information on drugs and working with drug manufacturers to withdraw drugs that cannot be used safely by physicians and their patients, ensuring the safest use of drugs that remain on the market is the greater challenge. Some adverse reactions are the result of medication errors related to circumstances outside of FDA jurisdiction, e.g., dispensing of drugs by pharmacists and prescribing by licensed health care providers regulated by the states. FDA recognizes that it has an important role to play in any larger process involving all interested parties, i.e., consumers, physicians, pharmacists, industry, and state regulators to address the challenge of ensuring the safest use of marketed drugs.

Once again, thank you for the opportunity to testify before the Committee today. I am happy to respond to questions.